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REMARKS

Status of the Claims

Claims 34-42 and 62-76 remain pending herein.

Claim Rejection under 35 U.S.C. 102

Claims 34-42 and 62-76 are rejected under 35 U.S.C. 102(a) as being unpatentable over O'Hagan et al., WO 00/50006 (O'Hagan II). Applicant respectfully traverses this rejection and its supporting remarks.

For a reference to anticipate a claim it must disclose each and every element of the claim. See MPEP 2131 and cases cited therein, especially *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989) and *In re Marshall*, 578 F.2d 301, 304, 198 U.S.P.Q. 344, 346 (CCPA 1978).

All presently pending claims concern microparticle compositions in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. As explained in the present specification at paragraph [0011] onwards, the inventors have unexpectedly found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished, for example, by separately providing a quantity of detergent at the time of macromolecule adsorption or by ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent (e.g., by not washing the microparticles or by a filtration step).

More particularly, the claims in the present application require (I) that the microparticles are subjected to a filtration step such that a particular percentage (i.e., about 10-90%, 10-60% or 25-40%) of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that a particular percentage (i.e., about 10-90%, 10-60% or 25-40%) of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

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O'Hagan II, however, does not teach or suggest a microparticle composition in which a particular percentage of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. As discussed in more detail below, it is not at all obvious to retain detergent in unbound form as claimed. In fact, as indicated in Singh et al. *infra* there is strong incentive to keep the detergent levels to a minimum (e.g., by a method such as centrifugation with washing).

With respect to limitation (II) above, which requires the absence of a washing step, O'Hagan II describes washing and centrifugation. See, for instance, Examples 1-3, pp. 46-47 (washed with water by centrifugation four times). As indicated in the present specification, such washing steps remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

With respect to limitation (I) above, the only discussion of a filtration step in O'Hagan II pertains to a size exclusion step in which microparticles are filtered through a 38 μ m mesh (which would have no effect on the bound and unbound detergent)—and this step is immediately followed by washing with water by centrifugation four times. See Examples 2, 3 and 27. Thus, O'Hagan II does not teach or suggest a filtration step like that claimed.

This is even more clearly apparent with respect to the cross-flow filtration step claimed in claim 36.

For at least the above reasons, it is respectfully submitted that O'Hagan II does not support a *prima facie* case of obviousness against claims 34-44 and 62-76. Reconsideration and withdrawal of the rejection of these claims over O'Hagan II are respectfully requested.

Claim Rejection under 35 U.S.C. 103-Levy in view of Paliard

Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of US 6,562,346 to Paliard et al. (Paliard). Applicant respectfully traverses this rejection and its supporting remarks.

Among other requirements, to establish a *prima facie* case of obviousness, the prior art reference (or references) must teach or suggest all the claim limitations. See, e.g., MPEP 706.02(j) and the cases cited therein. Levy and Paliard do not meet this threshold.

All claims require processes whereby macromolecules are adsorbed the microparticles. Levy, on the other hand, does not teach or suggest adsorption to microparticles, but rather is

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directed to improved methods for *incorporating* nucleic acids *into* polymeric microspheres and/or nanospheres (micro-encapsulation) through the use of a condensing agent. See, e.g., Abstract. See also the title of Levy: *Microspheres Containing Condensed Polyanionic Bioactive Agents and Methods for Their Production*.

See further the generic microsphere preparation method in Levy, Section 4.2, which states that the microspheres formed *contain* the bioactive agent:

In the standard embodiment ... at least one biocompatible biodegradable polymer is dissolved in a water-immiscible organic solvent to yield an organic phase. The hydrophilic bioactive agent [nucleic acid] is dissolved in water to yield a first aqueous phase, and the two phases are then emulsified to yield a water-in-oil (W/O) emulsion. A second aqueous phase is then formed... The W/O emulsion and the second aqueous phase are again emulsified to yield a double water-in-oil-in-water (W/O/W) emulsion. The organic solvent is then removed from the W/O/W emulsion, *yielding microspheres containing the hydrophilic bioactive agent....*

By contrast, in all presently pending claims, after removing the organic solvent from the emulsion to form microparticles in step (b), the biologically active macromolecule is added in step (c) such that it is *adsorbed* to the microparticle surface. Thus the teachings of Levy are not relevant to the pending claims and do not include the elements of the pending claims.

Furthermore, as noted above, all presently pending independent claims concern microparticle compositions in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. This feature of the invention is neither taught nor suggested by Levy.

More specifically, the independent claims in the present application require (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound and/or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. Among the independent claims rejected in view of Levy, claim 37 is directed to a method requiring limitation I, claim 39 is directed to a method requiring limitation II, and claim 34 is directed to a method requiring limitation I or II. Claim 42 is a product by process claim based on claim 34.

With respect to limitation (II) above, the Examiner argues that while the Examples of Levy require a washing step, other portions of Levy do not. Applicant has noted that, even assuming

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that portions of Levy do not explicitly set forth a washing step, one of ordinary skill in the art upon reviewing Levy would follow Levy's procedures, as set forth in the Examples, to produce microspheres. In particular, the Examples of Levy teach a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation, and washing recovered microspheres multiple times. See MPEP 2141.02.VI: A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Examiner has urged that "Levy does not specifically state that the microspheres formed are free of detergent; and it flows from one of the embodiment[s] that does not use a wash step but evaporates off the organic solvent (col. 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated." Applicant respectfully disagrees.

First, it is noted that the solvent evaporation step referred to by the Examiner is not an *alternative* to washing, as appears to be suggested by the Examiner, but rather is a process that is used to yield solid microparticles from a dispersed oil phase (i.e., one containing polymer and solvent) in a W/O/W emulsion. (When the solvent is evaporated solid polymer particles are left behind.)

Moreover, absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary would be motivated to wash the microparticles of excess detergent by centrifugation as taught by Levy. Indeed, as indicated in Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (of record—see the IDS filed 2/10/04), page 815, right column, third paragraph, there is motivation in the art to keep detergent levels, particularly cationic detergent levels, to a minimum.

Furthermore, even assuming for the sake of argument that Levy does not require a washing step, the absence of a washing step still would not necessarily produce the particular amounts of bound and unbound detergent claimed. The Examiner, on the other hand, urges that that this feature is inherent in Levy, that the PTO does not have a laboratory facility to provide factual evidence and that the applicant has not provided factual evidence that the particles of Levy contain less than the amount of detergent claims.

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With regard to inherency, it is initially pointed out that Levy *must* provide the claimed amounts of bound and unbound detergent. See MPEP 2112.IV (emphasis in original) (citations omitted):

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.... "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "...

The Examiner has pointed to Sections 4.2 and 4.6 of Levy as describing processes that do not require a washing step. Assuming solely for the sake of argument that these Sections describe processes in which the particles are not subjected to a washing step, it is clear that these processes will not necessarily produce the amount of bound and unbound detergent claimed. For example, in each of these processes the use of a detergent (emulsifying agent) is *optional*. See, col. 6, lines 50-52 and col. 12, lines 47-49.

Elsewhere, the microparticles are washed multiple times. It is noted in paragraph [0011] of the present specification that techniques in which microparticles are washed multiple times with water, such as the process of Levy, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles. This is a clear statement of fact, which is to be accepted by the Examiner, unless the Examiner has reason to doubt the objective truth of the same.

With regard to limitation (I) above (i.e., a step in which the microparticles are subjected to a filtration step such that a particular percentage of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound), it is first noted that Levy does not teach a filtration step.

The Examiner takes the position that filtration "appears to be equivalent to washing" and that, consequently, the filtration steps of claims 34 and 36 reads on the wash step of one of the embodiments of Levy at col. 13, line 5 (microspheres washed one or more times with water, Tris-EDTA, etc.), at col. 18, line 42 (washed three times with Tris-EDTA) and at col. 20, line 2 (this section reads on washing *cells*, rather than microspheres).

The Hawley's Condensed Dictionary entry previously cited by Applicant describes "filtration" as "[t]he operation of separating suspended solids from a liquid (or gas) by forcing the

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mixture through a porous barrier ...” The Examiner has focused on the first part of the definition (separating suspended solids from a liquid) in an attempt to have “filtration” read on the centrifugation step of Levy. However, because “filtration” further requires the use of a porous barrier (i.e., a *filter*), filtration is neither taught nor suggested by the washing steps Levy. As noted above, among other requirements, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the limitations of the claims.

Moreover, as noted above, the claimed amounts of bound and unbound detergent are neither taught nor suggested (inherently or otherwise) by Levy.¹

Finally, the Examiner argues that there is no demonstration in Applicant’s specification that not subjecting microparticles to a washing step or subjecting them to a cross-filtration step provides unusual/unexpected properties. Applicant disagrees. For example, as explained in the present specification at paragraph [0011] onwards, the inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished in several ways, including filtration and the avoidance of a washing step.

In summary, Levy neither teaches nor suggests the following: a method requiring macromolecule adsorption (all pending claims), a method requiring limitation I (see claims 36-38, 58, 59, 64, 65), a method requiring limitation II (see claims 39, 40, 60, 61, 66-69), or a method requiring limitation I or II (see claims 34, 35, 41, 43, 44, 62, 63, 70-76).

With regard to SDS (an anionic detergent), as previously noted, it is true that Levy discloses 0.1% SDS in Section 5.3.2. However, Levy’s use of SDS occurred *after* formation of DNA containing microspheres. In particular, at column 19, lines 8-10, Levy specifically teaches incubating DNA-containing microspheres in excess TE buffer with and without 0.1% SDS. At column 19, lines 11-13, Levy discloses that SDS was used to establish that charge-related associations between poly-L-lysine and DNA contribute to the DNA release and/or extraction

¹ In addition to ensuring that unbound detergent is made available for complex formation with macromolecules, the processes of the present invention are advantageous relative to those of Levy, *inter alia*, because they do not require a centrifugation step. This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a centrifugation step, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

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mechanism. Thus, in Section 5.3.2, the SDS is used as an *analytical reagent* to assess previously formed microspheres.

With respect to Paliard, this reference is cited for its disclosure of CTAB detergent, claimed in claims 38 and 40. Paliard, however, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, Paliard teaches washing in Example 5 (see col. 23, lines 53-55). "The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145.X.D.3. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Furthermore, because the SDS was used as an analytical reagent in Levy as noted above, the Examiner's assertion that it would have been obvious to use the CTAB of Paliard in place of the SDS of Levy is not persuasive.

Again, note that it is not at all obvious to retain detergent in unbound form as claimed. As indicated in Singh et al. *supra* (page 815, right column, third paragraph) there is strong incentive to keep the detergent levels to a minimum (e.g., by a method such as centrifugation with washing).

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 34-44 and 58-76.

Reconsideration and withdrawal of the rejection of the claims under U.S.C. 103(a) as unpatentable over Levy in view of Paliard are respectfully requested.

Claim Rejection under 35 U.S.C. 103-O'Hagan

Claims 34, 35, 36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,086,901 to O'Hagan et al. (O'Hagan). Applicant respectfully traverses this rejection and its supporting remarks.

As noted above, each of the claims in the present application requires (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound and/or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. Among the claims rejected in view of O'Hagan, claim 36 is directed to a method requiring limitation I, claims 34, 35 and 43 are directed

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to methods requiring limitation I or II, and claim 42 is a product by process claim based on claim 34.

With respect to limitation (II), O'Hagan describes washing and centrifugation. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation). This is noted by the Examiner, who urges that "there is no demonstration in applicant's specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles."

A couple of points are in order. First, the reason for not washing the microparticles is to ensure that a sufficient amount of unbound detergent is retained in the composition for complexation with macromolecules, which complexes provide unexpected properties. For example, as indicated in the present specification, the microparticles of the present invention adsorb such macromolecule/detergent complexes with high efficiency. See Summary of the Invention. Moreover, the inventors have discovered that these microparticles with adsorbed complexed macromolecules provide for superior immune responses. *Id.*

Second, as noted in paragraph [0011] of the present specification, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles. Thus O'Hagan further does not teach or suggest a process that produces the amount of bound and unbound detergent claimed.

Finally, unexpected results can, of course, be used to overcome a *prima facie* case of obviousness. See, e.g., MPEP 716.02(a)-(g). Here, however, a *prima facie* case has not been made out. In particular, O'Hagan further does not teach or suggest a process that produces the amount of bound and unbound detergent claimed. Nor does O'Hagan does not teach or suggest a process in which microparticles are not subjected to a washing step.

With respect to limitation (I), O'Hagan does not teach or suggest a filtration step at all, much less one that would provide bound and unbound detergent in the amounts claimed.

This is even more clearly apparent with respect to the cross-flow filtration step claimed in claim 36. In this regard, the Examiner argues that the process of claim 36 "reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and the removal of the water appears to approximate the process of filtration/washing." As with Levy,

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however, the washing steps of O'Hagan (which are performed in conjunction with centrifugation) have nothing to do with filtration, which as noted above involves the use of porous barrier (i.e., a filter) to separate suspended solids from a liquid. Claim 36 is even more remote from O'Hagan, because it involves a particular type of filtration.

The has Examiner correctly noted that claim 42 is a product by process claim. Nonetheless, claim 42 is unobvious over O'Hagan, because O'Hagan neither teaches nor suggests a method which produces the amounts of bound and unbound detergent claimed.

As noted above, it is not at all obvious to retain detergent in unbound form as claimed. As indicated in Singh et al. *supra* there is strong incentive to keep the detergent levels to a minimum (e.g., by a method such as centrifugation with washing).

For at least the above reasons, it is respectfully submitted that O'Hagan does not support a *prima facie* case of obviousness against claims 34-36 and 42. Reconsideration and withdrawal of the rejection of these claims over O'Hagan are respectfully requested.

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

FEES

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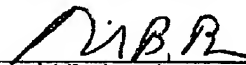
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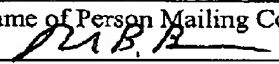
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